THE EFFECT OF CIMETIDINE ON SERUM CONCENTRATIONS OF PIROXICAM

by

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A project submitted to the faculty of the
University of Utah in partial fulfillment of the requirements
for the degree of

Doctor of Pharmacy

College of Pharmacy
University of Utah

May 1985

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of Claude Mailhot in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

5/16/95
Date

Chairman, Supervisory Committee

Approved for the Department of Pharmacy Practice

Approved for the Doctor of Pharmacy Committee

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Claude Mailhot

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

May 16, 1985
Date

Chairman, Supervisory Committee

May 16, 1985
Date

Member, Supervisory Committee

May 8, 1985
Date

Member, Supervisory Committee

ACKNOWLEDGEMENTS

I wish to thank:

my supervisory committee, Stephen Dahl, Jean Devenport, and John Ward, for their time, help and advice,

the ten volunteers who completed the study, for their compulsive participation,

Ray Galinsky, for his assistance with the pharmacokinetic evaluations,

Linda Strand, for her assistance with the statistical analyses,

the Rheumatology Division for partially funding this study and the staff for their collaboration,

Pfizer Laboratories for performing the piroxicam assay,

Smith Kline & French Laboratories for graciously providing cimetidine,

and Susan Havlicak for typing this manuscript.

I am sincerely grateful to my husband, Pierre, for his support, encouragement and patience during these last two years.

To all of you, Thank You.

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INTRODUCTION

Drug interactions are a major factor in the etiology of adverse drug reactions.[1] Because patients often take more than one medication, the possibility of a patient experiencing an adverse drug interaction is of concern. Numerous drug interactions caused by cimetidine, a potent H_2 receptor antagonist, have been documented in humans. Cimetidine has been shown to decrease the elimination of a variety of drugs including, antipyrine[2-4], aminopyrine[5], chlordiazepoxide[6,7], diazepam[8-10], warfarin[11-13], theophylline[2,14-21], quinidine[22-23], carbamazepine[24], and phenytoin[25-28]. All of the above mentioned drugs are eliminated after metabolism by mixed function oxidases in the liver, suggesting that cimetidine inhibits the action of the cytochrome P-450 oxidative enzymes.

Piroxicam is a recently introduced non-steroidal anti-inflammatory drug (NSAID) belonging to a novel chemical group, the oxicams. Clinical studies indicate that piroxicam is safe and effective in long term management of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.[29-33] The elimination half-life of piroxicam is prolonged: in pharmacokinetic studies, the mean half-life ranged from 37.5 to 60.4 hours (range 14-158 hours) in healthy subjects.[34-41] Despite this wide inter-individual range, the half-life within an individual appears constant.[37]

Piroxicam is metabolized in man primarily by 5'-pyridine ring hydroxylation followed by glucuronidation.[42] The metabolites of piroxicam have little or no anti-inflammatory activity in animal models.[43] The metabolites have also been shown to be inactive as

inhibitors of cyclo-oxygenase in tissue preparations in which piroxicam showed potent inhibitory activity.[36]

Since the main metabolic pathway of piroxicam is hydroxylation, a reaction generally dependent on the hepatic cytochrome system, piroxicam is potentially susceptible to interventions that alter liver metabolic activity such as concurrent cimetidine administration.

In patients treated with piroxicam, the gastrointestinal system appears to be the predominant site of adverse effects.[44-46] These effects include epigastric and abdominal pain, nausea and vomiting, melena, hematemesis, and peptic ulcer. Because of the nature of the side effects, the concomitant use of cimetidine and piroxicam is likely.

Depression of renal function has been associated with piroxicam[47,48] and with other NSAIDs[49-52]. Hemodynamic changes secondary to prostaglandin synthesis inhibition have been proposed as a mechanism for the depression in renal function observed with the NSAIDs.[52-55] Patients at risk are those with underlying intrinsic renal disease, with or without obvious renal insufficiency, and patients with decreased effective renal plasma flow due to such conditions as volume contraction, congestive heart failure, and liver disease with ascites. Additional risk factors include advanced age and concurrent use of diuretics.[47-56]

Assuming that the hydroxylation of piroxicam is cytochrome P-450 mediated, the addition of cimetidine to the therapeutic regimen of a patient on piroxicam could result in a decrease in piroxicam elimination and prolongation of its effect. Prolongation of the anti-

prostaglandin effect is of clinical concern because it may increase the hazard of renal dysfunction in patients at risk.

The purpose of this study was to determine if serum concentrations of piroxicam following a single oral dose are altered by previous and concurrent administration of cimetidine.

MATERIALS AND METHODS

The protocol and the consent form were approved by the University of Utah Institutional Review Board.

Subject Selection

Twelve healthy male volunteers consented in writing to participate in the study. Subjects were admitted to the study if 1) they had a normal clinical and laboratory examination, 2) they did not use tobacco, 3) their weight was within 25% of their ideal body weight, 4) they had not used any medication or alcohol within the previous 2 weeks, 5) they showed willingness and ability to perform the tasks necessary for the study.

Subjects were excluded for the presence or history of hypersensitivity to aspirin, piroxicam or cimetidine. No alcohol or medication was permitted during the study.

Before entry into the study each subject underwent laboratory examination and clinical assessment including medical and medication histories and a physical examination. A copy of the consent form and of the form used to collect the clinical assessment data are included in Appendix 1.

The laboratory examination included a complete blood count with differential and platelets, urinalysis, blood chemistry profile i.e., sodium, chloride, potassium, carbon dioxide, urea nitrogen, glucose, creatinine, uric acid, calcium, phosphate, total and direct bilirubin, total protein, albumin, cholesterol, gammaglutamyltransferase, alkaline phosphatase, lactic dehydrogenase, aspartate aminotransferase, and alanine aminotransferase.

Study Plan

The study was conducted at the University of Utah Hospital Rheumatology clinic. On the first day of the study, following an overnight fast, each subject received 20 mg of piroxicam (Feldene®, Pfizer Laboratories; New York, NY) orally as a single dose with 180 ml of water. Subjects ingested a standard breakfast one hour after the administration of piroxicam. Venous blood samples were collected according to the schedule described in the section sample collection. Subjects began urine collection in 24 hour aliquots for seven days following the piroxicam dose (see Sample Collection).

On day 7, each subject received 56 tablets of cimetidine 300 mg (Tagamet®, Smith Kline and French Laboratories; Philadelphia, PA) with instructions to take one tablet four times a day with meals and at bedtime for 14 days, starting on day 8 of the study.

On day 15 of the study, seven days after the initiation of cimetidine, each subject, once again, received 20 mg of piroxicam orally. Blood and urine samples were collected in the same fashion as after the first dose. Cimetidine administration was continued throughout blood and urine collection. Figure 1 illustrates the study design.

Subjects were interviewed for possible adverse reactions at least twice during the study period. Adverse reaction forms were completed by the investigator after each interview (see Appendix 2). Subjects were asked to keep a record of compliance and adverse effects during cimetidine administration (see Appendix 3). Compliance was also assessed by interview and capsule count, both performed twice during the study period.

Sample Collection

Venous blood samples were collected into red top Vacutainers® (Vacutainer System, Rutherford, NJ) from an antecubital vein by venipuncture or through a cannula. The cannula used for the first 11 to 12 samples was kept patent by the instillation of 2 ml of heparin (100 units/ml) after each blood draw or every hour whichever came first. Seven milliliter blood samples were collected at the following times relative to piroxicam ingestion: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 34, 48, 58, 72, 96 and 168 hours.

The blood was allowed to clot and was then centrifuged at 3780 rpm for six minutes. The serum was collected from each specimen and stored at -20°C pending analysis.

Urine was collected into sterile plastic bags (Whirl-Pak®, Nasco; Modesto, CA) or plastic containers in 24 hour aliquots for seven days after piroxicam dose. Urine was kept refrigerated until measurement. The total volume of each 24 hour period was pooled and measured daily. For each 24 hour aliquot, 60 ml sample was collected and stored at -20°C. Appendix 4 contains a copy of the blood and urine collection forms.

Piroxicam Analysis

The serum samples were analyzed for piroxicam concentration by high-performance liquid chromatography. The assay was performed by Pfizer Laboratories using the method of Twomey et al.[57] The method sensitivity limit is 0.5 mcg/ml. A 5 mcg/ml control sample which was run with each assay showed a standard deviation of 0.2 mcg/ml and a coefficient of variation of 4.7 percent. Cimetidine does not interfere with the piroxicam assay.[58]

Pharmacokinetic Description and Calculation

For each subject, the elimination rate constant (kel), half-life (t1/2), and area under the serum concentration versus time curve (AUC) were calculated using piroxicam concentrations obtained before and after cimetidine administration. The equations used to obtain these parameters are included in Appendix 5.

The piroxicam serum concentration-time data were plotted on semi-logarithmic graph paper. The elimination rate constant (kel) was obtained from least squares regression of the data points between the 12 hour concentration and the last measurable serum concentration. The half-life was calculated from the elimination rate constant.

The area under the curve was calculated using the trapezoidal method. As recommended by Chiou,[59] the linear trapezoidal method was used for pre-peak and plateau data and the logarithmic trapezoidal method was used for the post-peak or post-plateau data. The remaining area from the last measurable point to infinity was calculated by dividing the concentration at the last time point by kel. The total area was the sum of the results of these three determinations.

Statistical Analysis

Due to the small sample size, a nonparametric test was used to analyze the pharmacokinetic changes. The Wilcoxon matched-pairs signed-ranks two-tailed test with an alpha level of 0.05 for significance was chosen.

RESULTS

Of the twelve healthy male volunteers admitted to the study, ten completed the study. The mean age was 27 years with a range of 23 to 35 years. The mean weight was 79.7 kilograms, and ranged from 65.9 to 100 kilograms. One volunteer (#010) suffered from a cold and was excluded because he had to use medications. Another volunteer (#012) discontinued the study because he did not tolerate the venipunctures.

The piroxicam plasma concentration-time profiles with and without cimetidine treatment are illustrated for each volunteer in Figures 2 to 11. The calculated elimination rate constants (kel) and half-lives (t1/2) for each volunteer are shown in Tables 1 and 2, respectively. The percent change between kel and t1/2 values calculated before and after cimetidine administration revealed a large inter-subject variation. Kel changes ranged from -24% to +13.6% and t1/2 changes ranged from -11.9% to +31.7%.

The mean (± standard deviation) elimination rate constant for piroxicam declined from 0.0149 ± 0.0036 $hours^{-1}$ to 0.0139 ± 0.0035 $hours^{-1}$ following the administration of cimetidine. The mean (±SD) half-life before and after cimetidine was 49.9 ± 15.5 hours and 53.4 ± 16.5 hours, respectively. These results were not statistically significant ($P > 0.05$). The Type II error was estimated to be 24% for these two parameters.

The calculated area under the piroxicam serum concentration-time curve (AUC) before and after cimetidine are summarized in Table 3. For all subjects but one the AUC was greater after cimetidine administration, resulting in a statistically significant 15.5%

(range: -2.4% to 29.5%) increase in AUC from 144.52 to 168.02 mg-hours/L ($p = 0.009$).

Coefficients of determination were calculated from the least square regression lines used to calculate the elimination rate constants. Their values ranged from 0.80 to 0.99 with a mean of 0.90.

Compliance assessed by interviews, capsule counts, and diary entries was 100% in five volunteers, 98.2% in three volunteers, and 96.4% in two volunteers.

The following adverse reactions were reported by the volunteers during cimetidine administration: flatus (5), diarrhea (2), headache (2), nausea (1), anorexia (1), and fatigue (1). The number of volunteers who experienced the adverse reactions appears in parentheses. None of the volunteers experienced additional adverse reactions when piroxicam was added to cimetidine.

DISCUSSION

The pharmacokinetic parameters of piroxicam obtained before the administration of cimetidine were compared to values reported in the literature in similar populations. Other studies have reported mean half-lives ranging from 37.5 to 60.4 hours[34-41] compared to the mean half-life of 49.8 hours in the present study. Mean areas under the piroxicam serum concentration-time curve from time zero to infinity after a 20 mg oral dose varied from 100.6 to 169 mg-hours/L compared to the mean of 144.5 obtained in this study.[34-41] Although statistical analysis was not used in comparing these values, it appears that the pharmacokinetic values obtained from this study are within the range of those reported in other studies.

Cimetidine decreases the elimination of a large number of drugs metabolized by hepatic mixed function oxidases. This effect is probably due to inhibition of cytochrome P-450 in hepatic microsomes.[60-67] Piroxicam is metabolized in the liver by hydroxylation followed by glucuronidation.[42] In this study, the administration of cimetidine did not significantly change the piroxicam elimination rate from the serum in the majority of subjects.

It is well known that the clearance rate of drugs primarily eliminated by microsomal metabolism is highly variable among patients. One source of variability is the recent recognition of multiple forms of cytochrome P-450.[67-70] These cytochrome P-450 isoenzymes vary in their metabolizing activity for a given substrate and exhibit varying degrees of overlapping substrate activity. Recent studies with rat liver microsomes identified two different

cytochrome P-450 isoenzymes capable of binding cimetidine: one with a high affinity binding site and one with a low affinity binding site.[67] Assuming similar findings in humans, it is possible that piroxicam is metabolized by the low affinity cytochrome P-450 isoenzyme, explaining the absence of effect of cimetidine on kel in the majority of our subjects. Since we did not measure the urinary metabolites of piroxicam we are unable to determine if there is any change in the pattern of metabolite formation when cimetidine is given with piroxicam.

The lack of a statistically significant difference between the pre- and post-cimetidine elimination rate constants was probably not an artifact since the Type II error was within an acceptable range (i.e. 24%). Thus, the likelihood of missing an important effect on kel is unlikely.

Although the elimination rate constants were not significantly different, the calculated AUCs were significantly increased after cimetidine administration. AUC is directly proportional to bioavailability and dose, and is inversely related to elimination rate constant (kel) and apparent volume of distribution (Vd). Since the piroxicam dose given on both occasions was the same, the observed increase in AUC could be explained by an increase in the bioavailability, a decrease in Vd or kel, or a combined effect of these factors.

Cimetidine-induced alterations of gastric pH may increase bioavailability. According to the Henderson-Hasselbach equation, elevation of gastric pH by cimetidine would increase the ionization of weak acids; therefore, dissolution would be enhanced. Assuming an

accelerated dissolution of piroxicam, a weak acid, following cimetidine administration, subsequent absorption of piroxicam from the intestine possibly could be increased. However, administration of antacids does not modify the pharmacokinetics of piroxicam.[35]

A decrease in Vd possibly could be explained by tissue binding displacement. Displacement of drugs from tissue binding sites by cimetidine is possible since its steady-state volume of distribution is 0.8 to 1.2 liter/kg,[71-73] and a large fraction of the cimetidine dose distributes into skeletal muscles.[74] Because piroxicam has an apparent Vd of 0.12 to 0.16 liter/kg,[36] which is approximately the volume of the extracellular fluid compartment, it is unlikely that tissue binding displacement would be significant.

Although the elimination rate constants before and after cimetidine were not significantly different, there was a trend toward a decrease in kel after cimetidine administration. This may also contribute to the observed increase in AUC after cimetidine administration. However, the statistically significant increase in AUC (mean: 15%) observed in this study is probably not clinically significant.

When the plasma concentration-time profiles were examined, more than one peak of drug concentration was revealed. This may indicate enterohepatic recirculation of piroxicam as proposed by other investigators.[38,40,41]

This study demonstrated that cimetidine administration slightly but significantly increased the area under the piroxicam concentration versus time curve, in ten young and healthy males. Cimetidine administration did not affect the elimination rate constant or the

half-life of piroxicam in the same subjects. The results of this study suggest that cimetidine does not alter the elimination kinetics of a single dose of piroxicam in young healthy males.

FIGURES

STUDY FLOW CHART

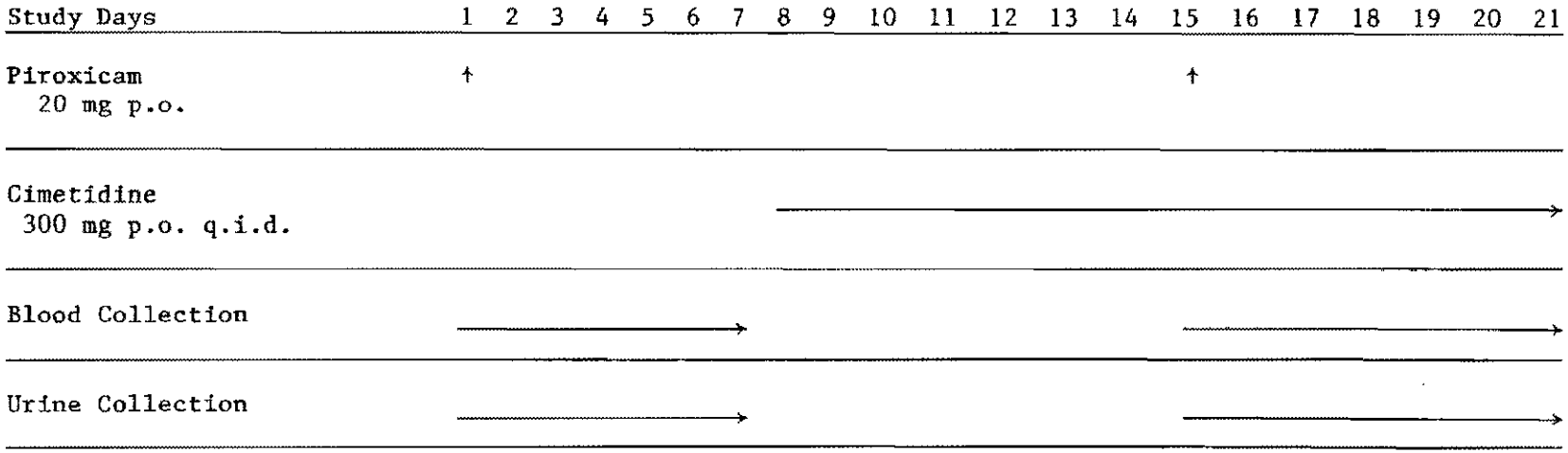

Figure 1: Study Design

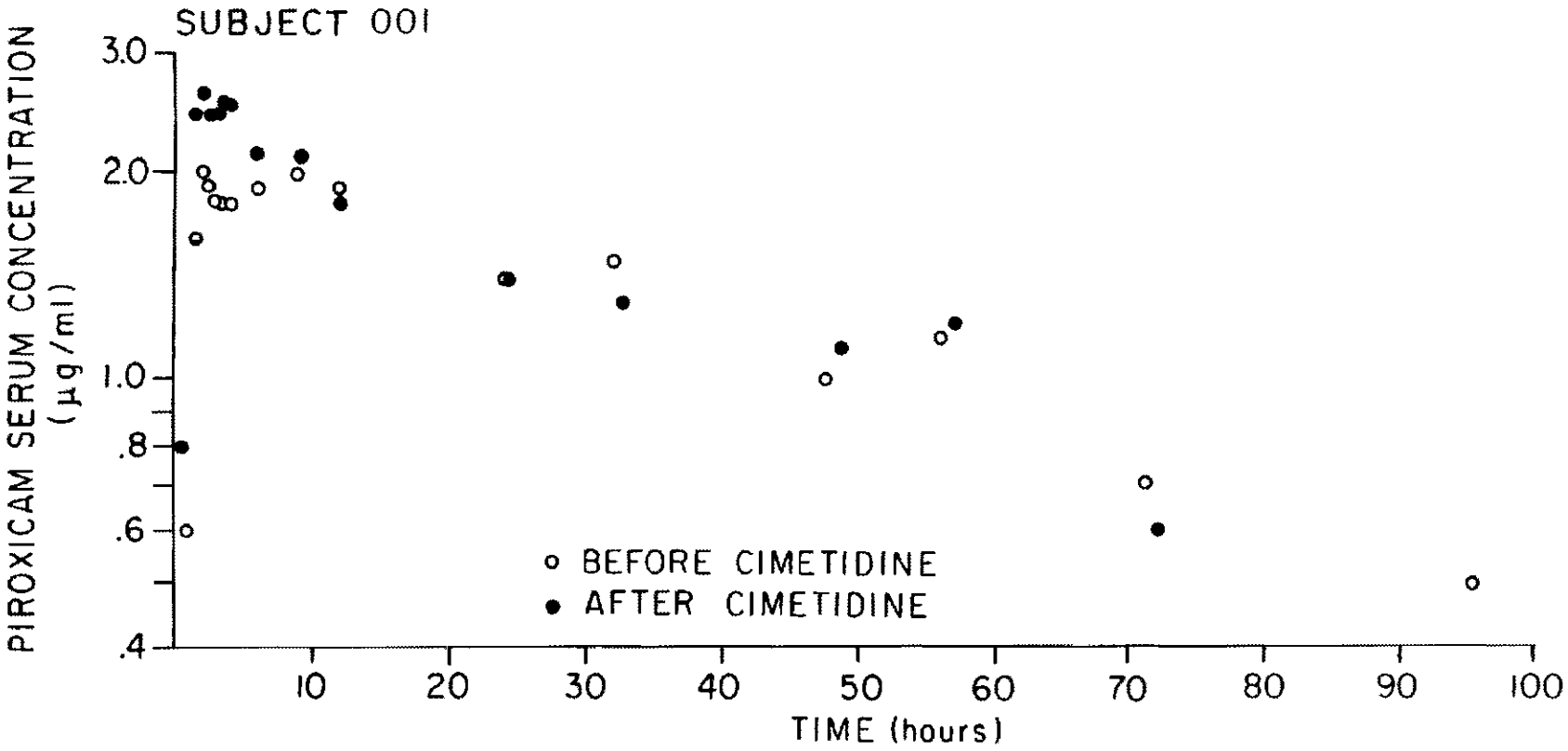

Figure 2: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #1

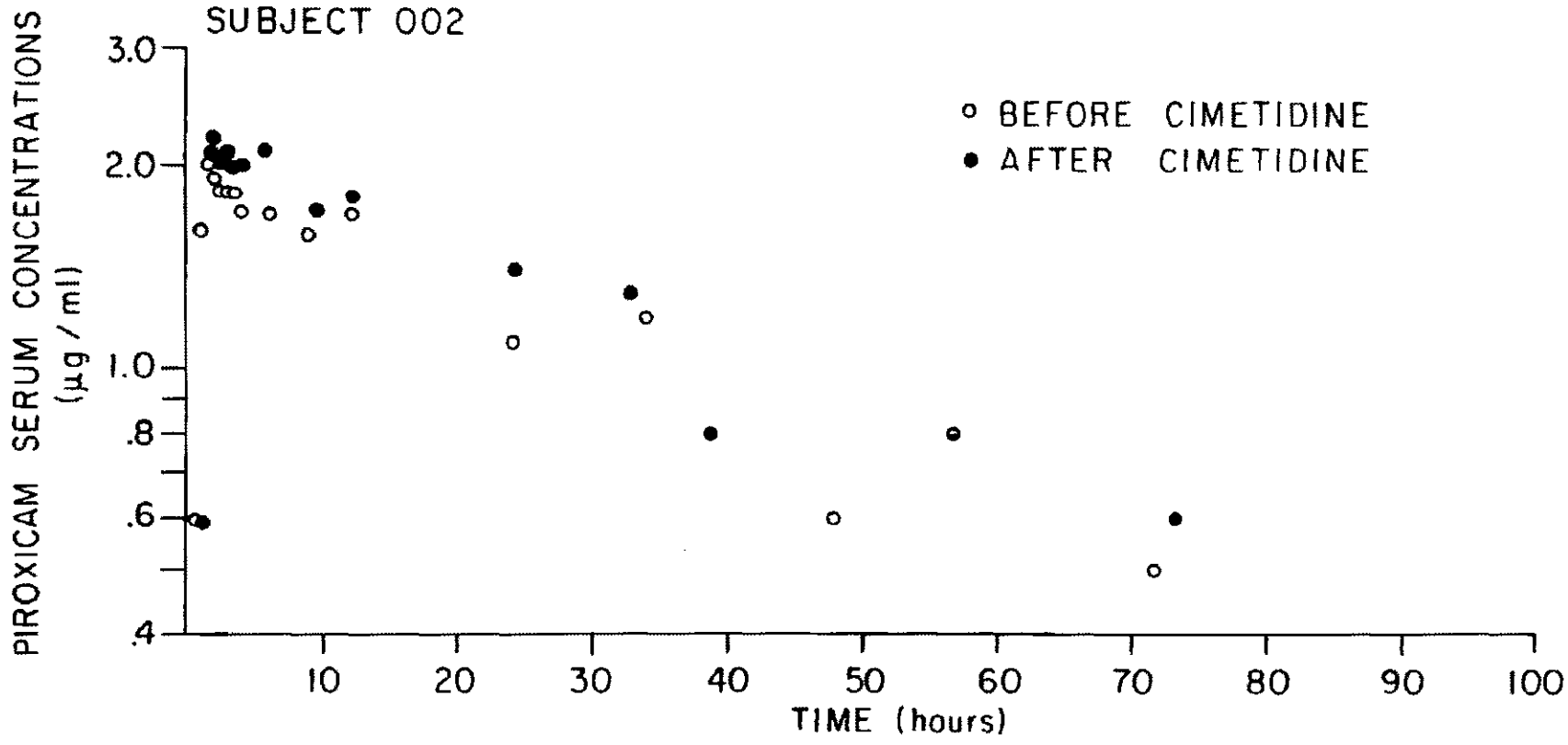

Figure 3: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #2

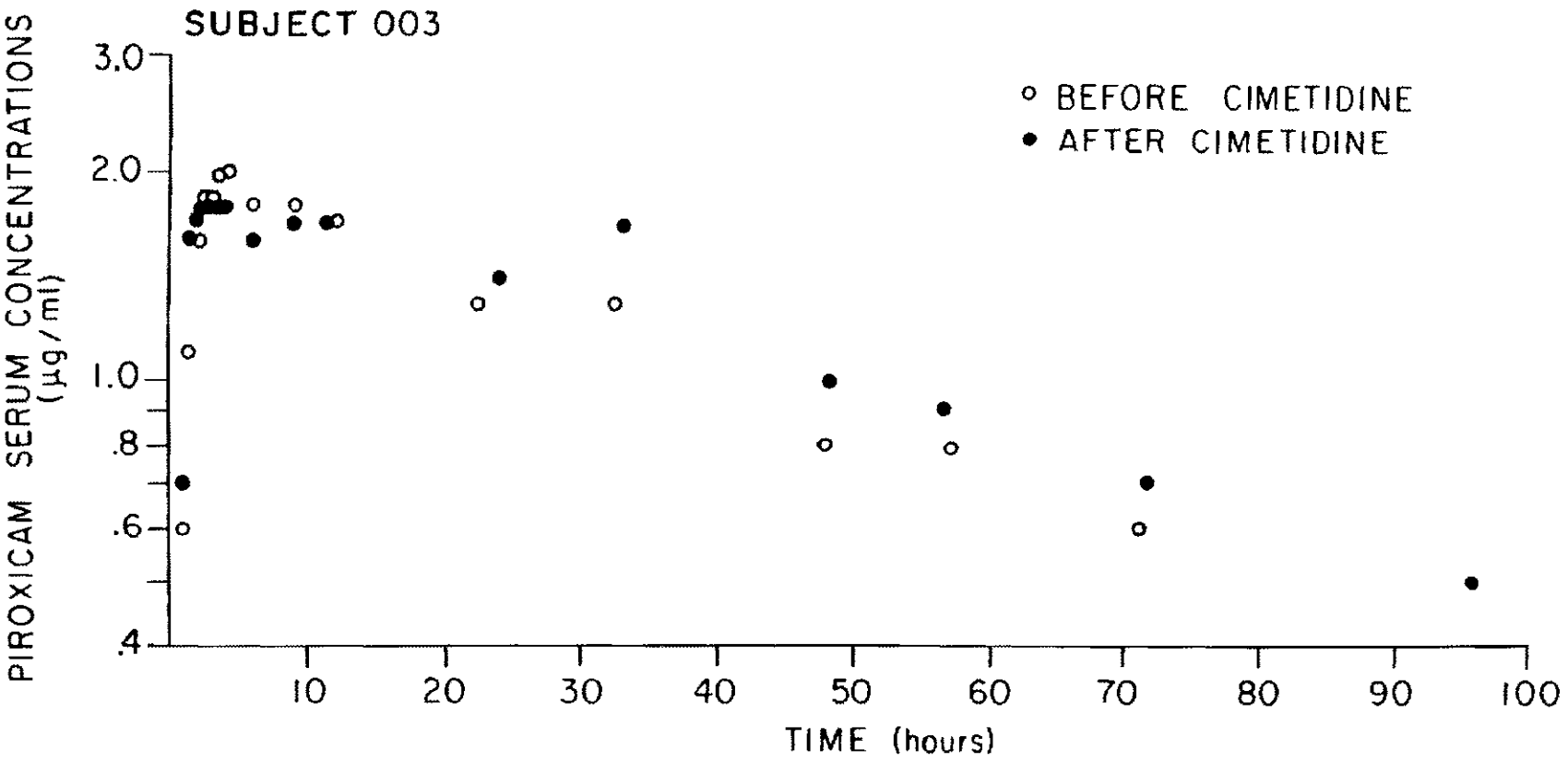

Figure 4: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #3

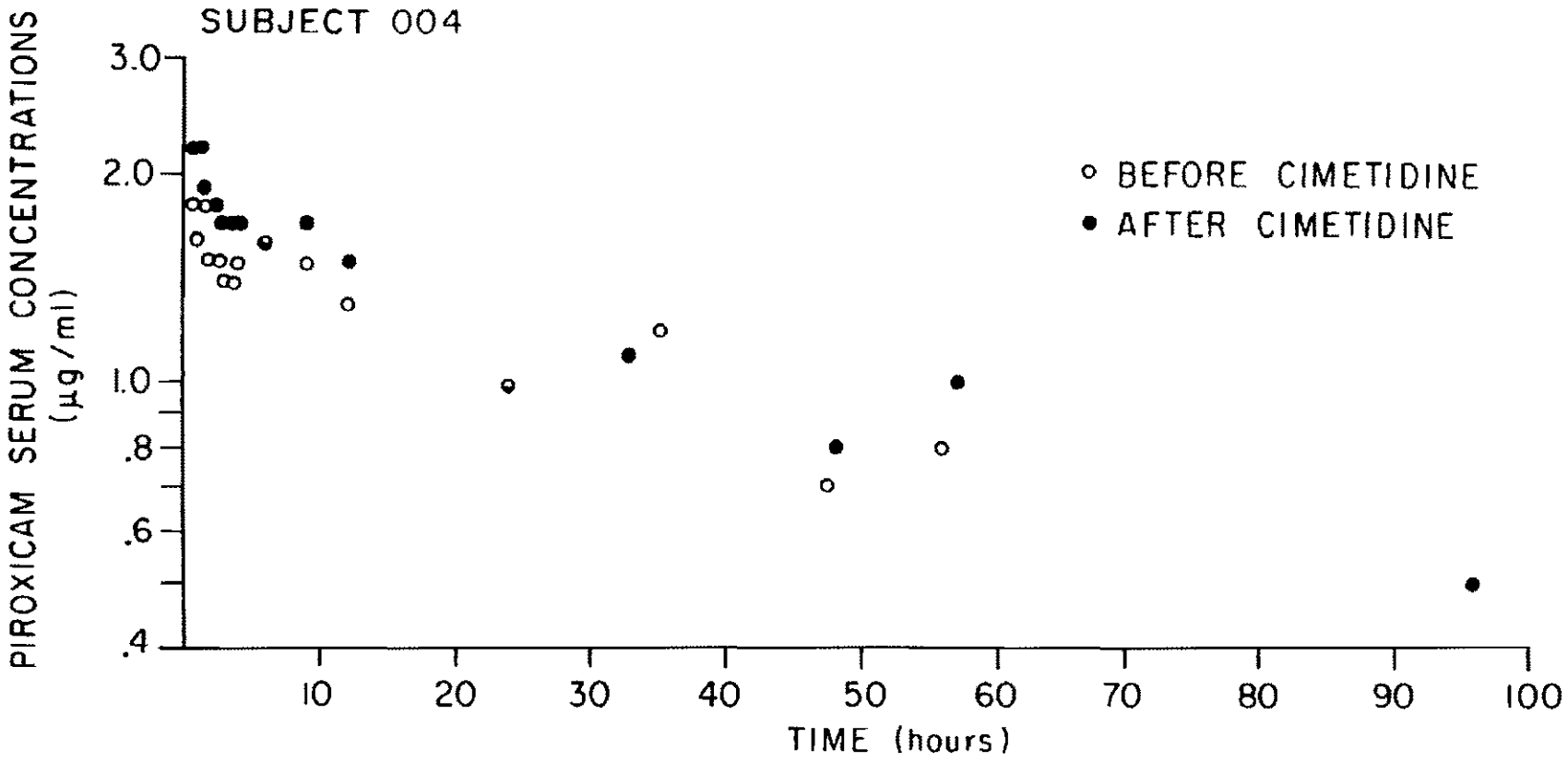

Figure 5: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #4

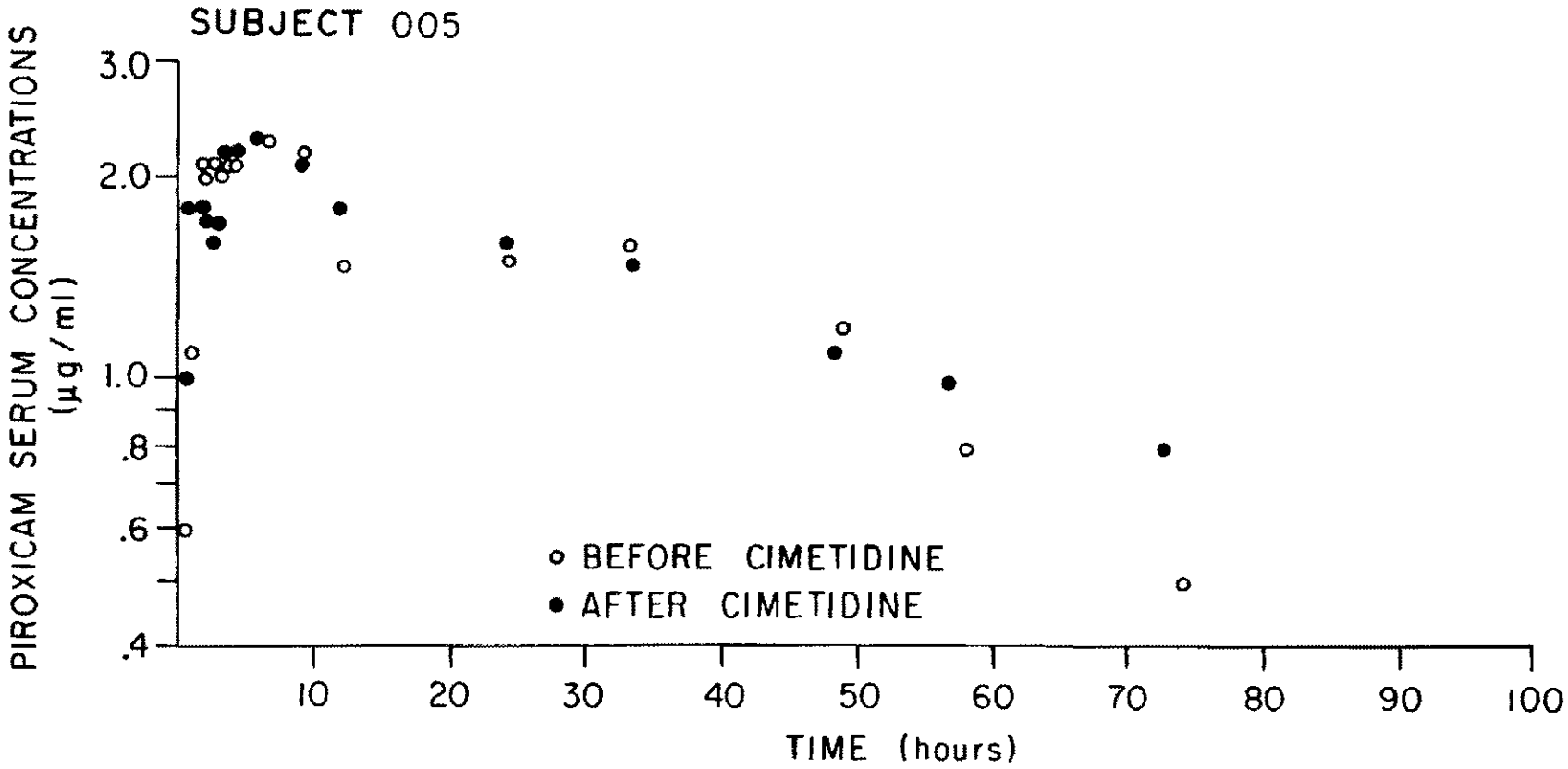

Figure 6: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #5

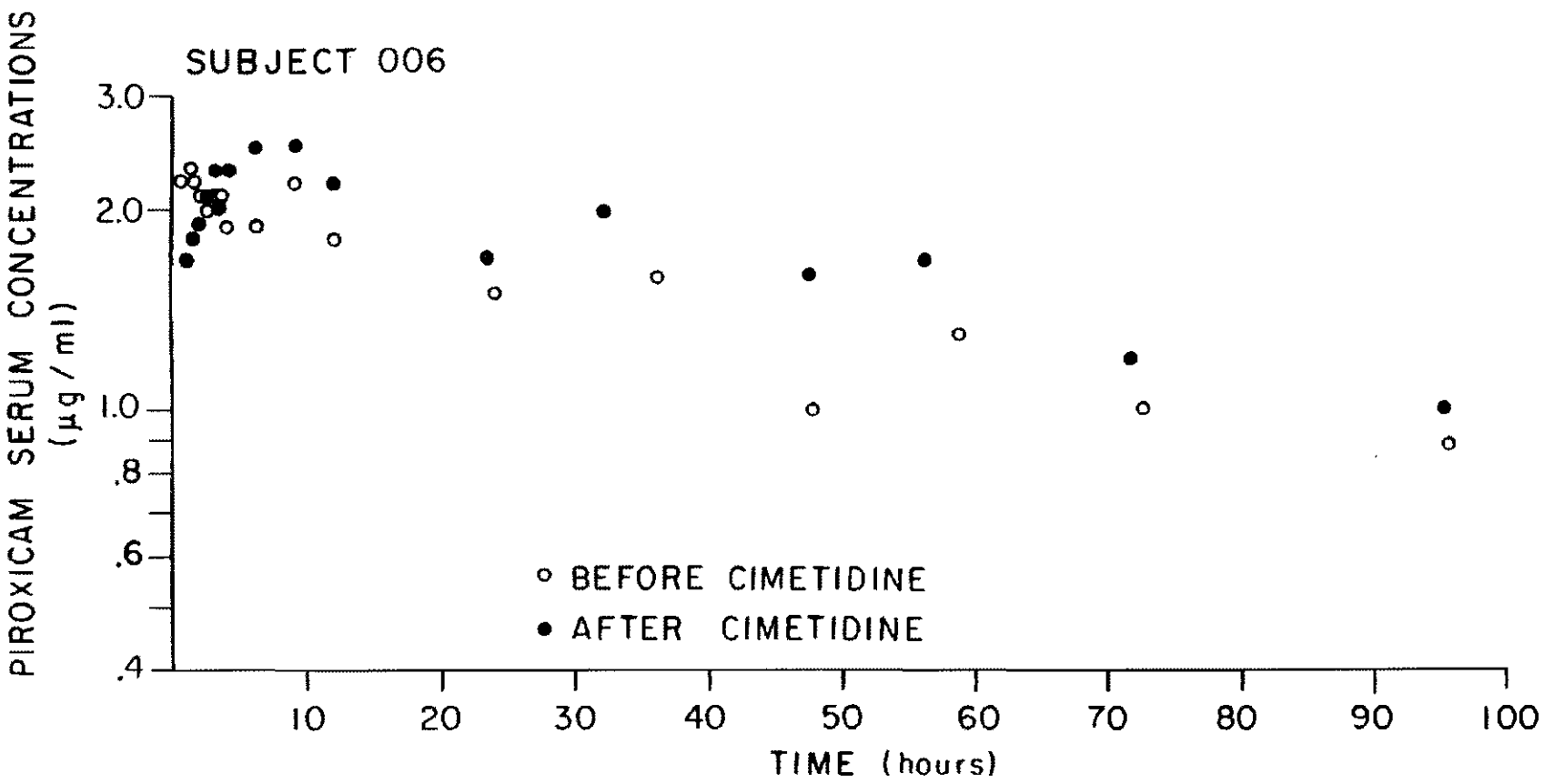

Figure 7: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #6

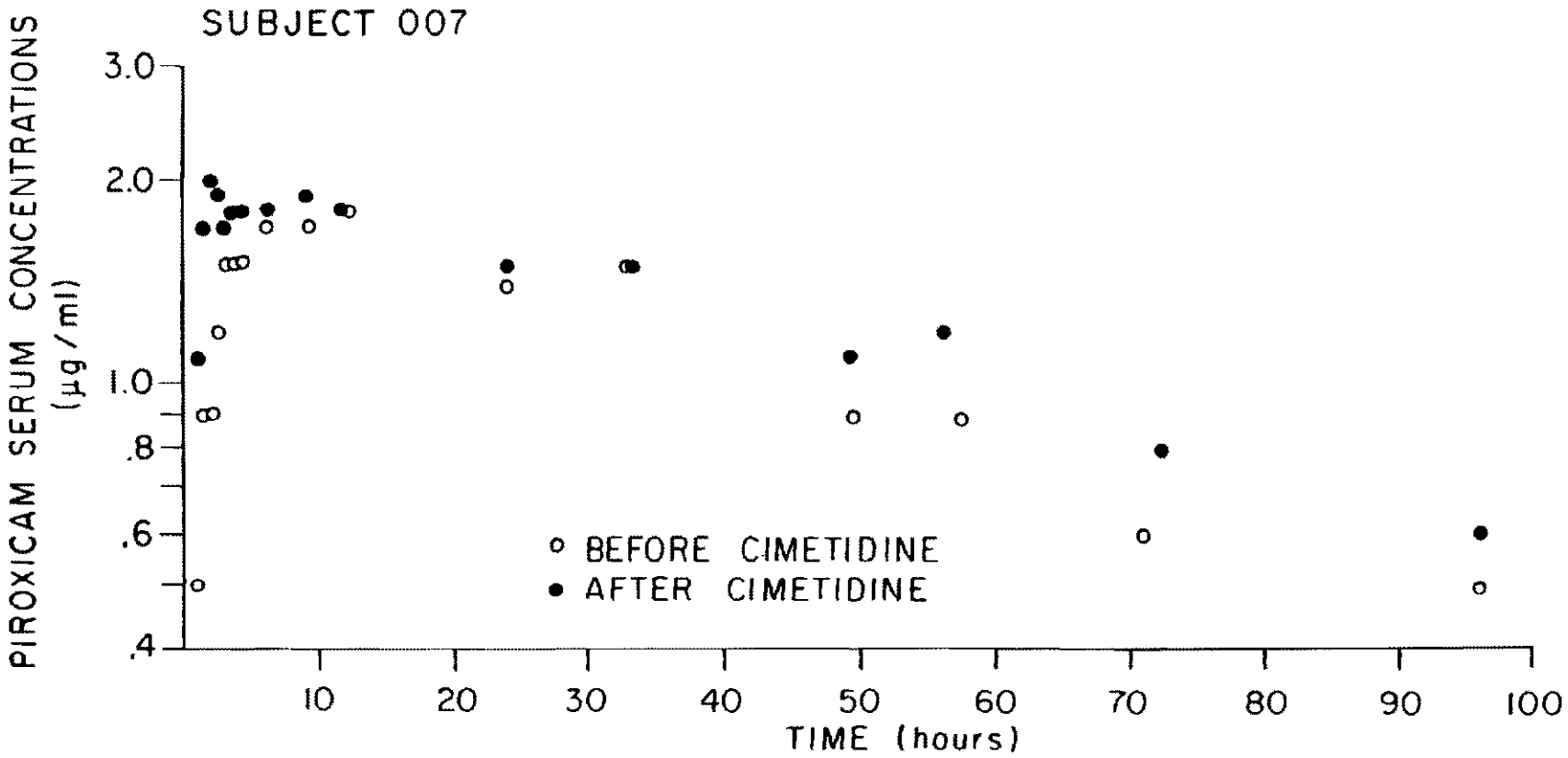

Figure 8: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #7

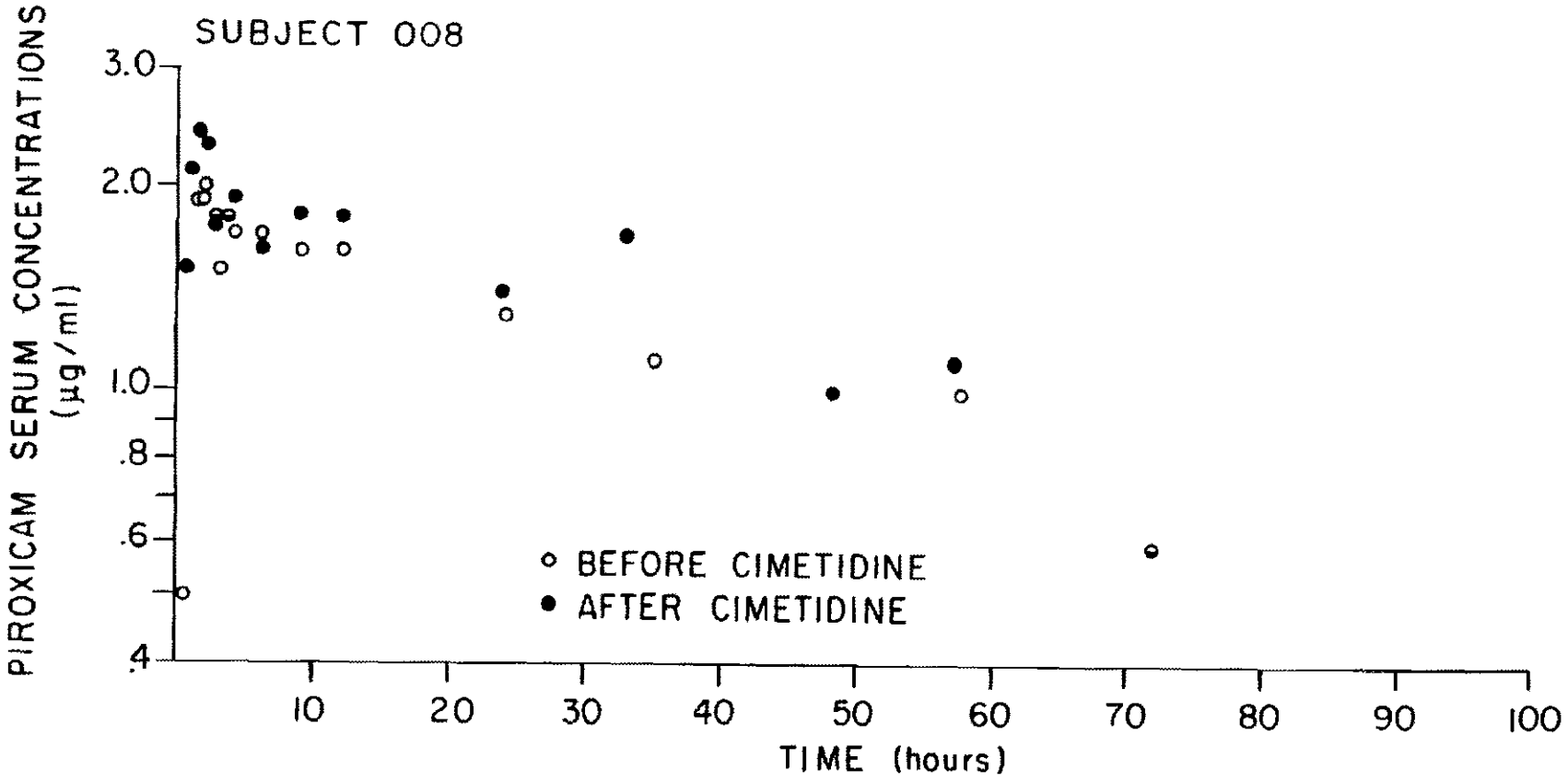

Figure 9: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #8

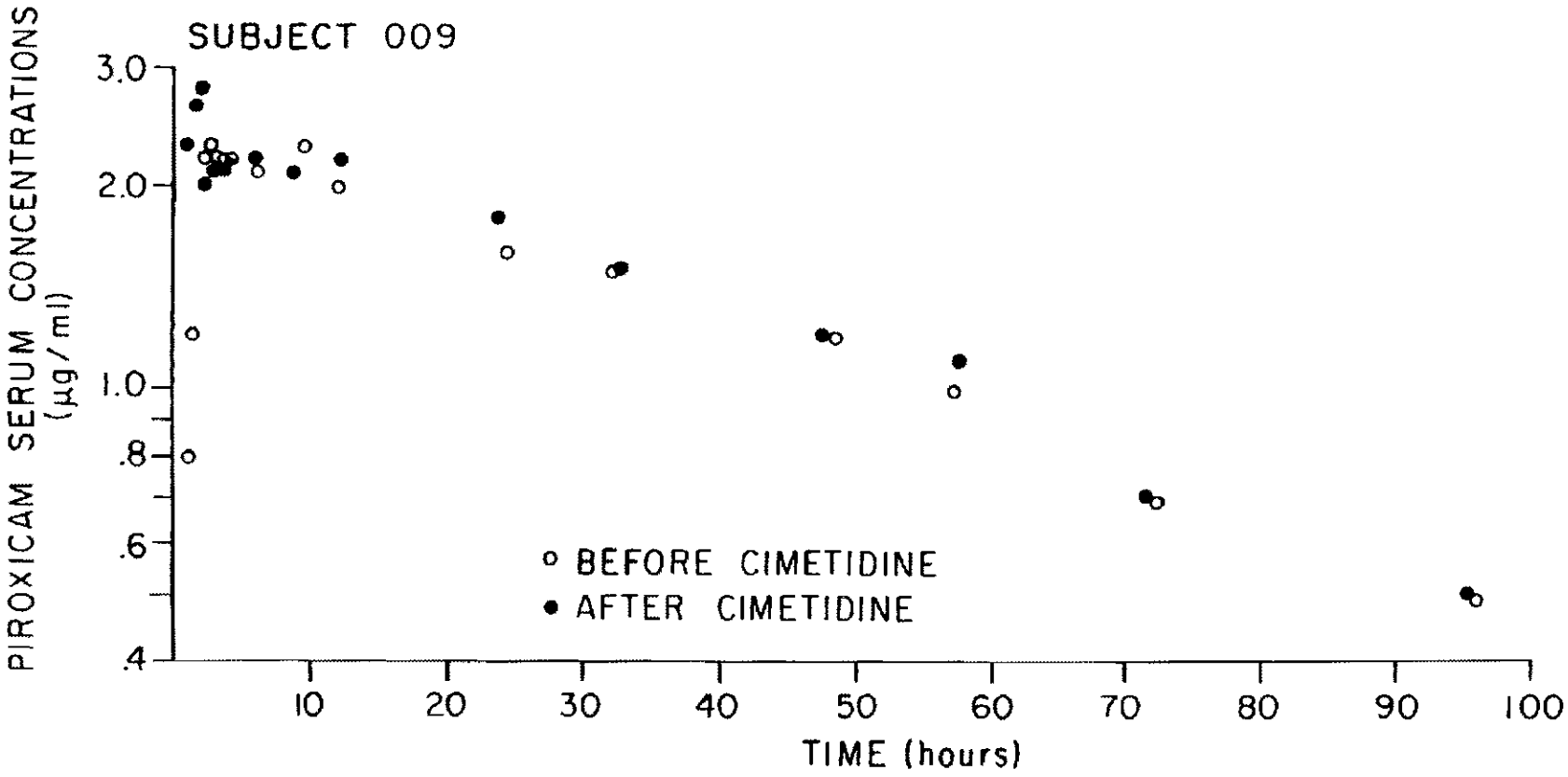

Figure 10: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #9

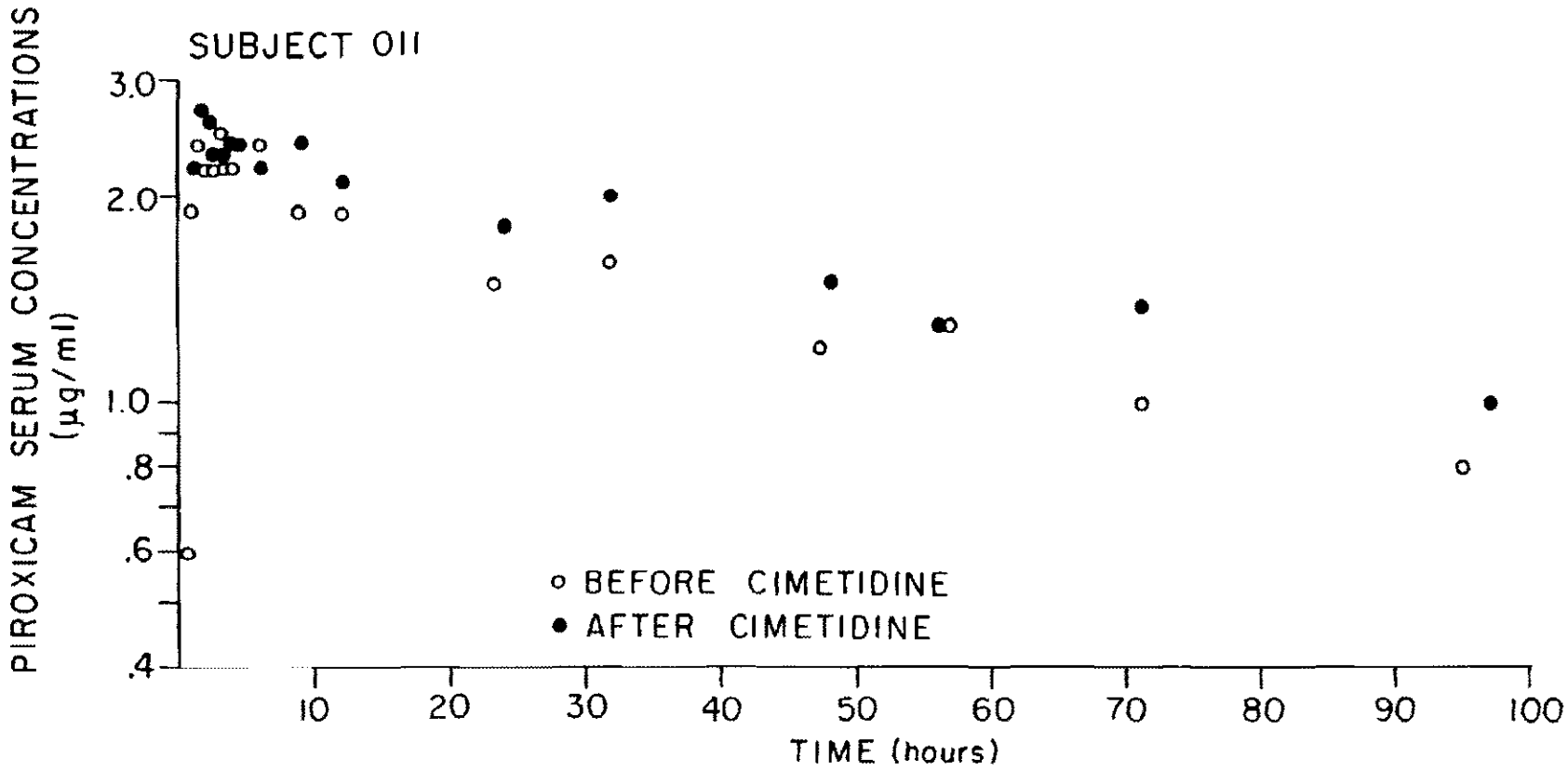

Figure 11: Semi-Logarithmic Graph of Piroxicam Serum Concentration Versus Time for Subject #11

TABLES

TABLE 1

ELIMINATION RATE CONSTANT (Kel) OF PIROXICAM

BEFORE AND AFTER CIMETIDINE ADMINISTRATION

SUBJECT NUMBER	Kel before cimetidine ($Hours^{-1}$)	Kel after cimetidine ($Hours^{-1}$)	PERCENT CHANGE %
1	0.0154	0.0150	- 2.6
2	0.0192	0.0184	- 4.2
3	0.0175	0.0154	-12.0
4	0.0127	0.0120	- 5.5
5	0.0183	0.0139	-24.0
6	0.0083	0.0083	0
7	0.0162	0.0131	-19.1
8	0.0147	0.0167	+13.6
9	0.0167	0.0179	+ 7.2
11	0.0098	0.0085	-13.3
Mean	0.0149	0.0139	- 5.9
Standard Deviation	0.0036	0.0035	

p value = 0.135

TABLE 2

HALF-LIFE (t1/2) OF PIROXICAM BEFORE AND AFTER CIMETIDINE ADMINISTRATION

SUBJECT NUMBER	t 1/2 before cimetidine (HOURS)	t 1/2 after cimetidine (HOURS)	PERCENT CHANGE %
1	45.0	46.2	+ 2.7
2	36.1	37.7	+ 4.4
3	39.6	45.0	+13.6
4	54.6	57.8	+ 5.8
5	37.8	49.8	+31.7
6	83.5	83.5	0
7	42.8	52.9	+23.6
8	47.1	41.5	-11.9
9	41.5	38.7	- 6.7
11	70.7	81.5	+15.3
Mean	49.9	53.4	+ 7.8
Standard Deviation	15.6	16.5	

p value = 0.106

TABLE 3

AREA UNDER THE PIROXICAM SERUM CONCENTRATION VERSUS TIME CURVE (AUC)

BEFORE AND AFTER CIMETIDINE ADMINISTRATION

SUBJECT NUMBER	AUC before cimetidine (mg-hours/L)	AUC after cimetidine (mg-hours/L)	PERCENT CHANGE %
1	142.2	138.8	- 2.4
2	100.8	118.4	+17.5
3	115.5	137.9	+19.4
4	119.2	132.2	+10.9
5	123.6	158.0	+27.8
6	235.6	282.3	+19.8
7	130.2	160.5	+23.3
8	122.8	131.8	+ 7.3
9	146.0	149.3	+ 2.3
11	209.3	271.0	+29.5
Mean	144.5	168.0	+15.5
Standard Deviation	43.5	58.7	

p value = 0.009

APPENDIX 1

PATIENT CONSENT FORM

DATE _____

Study Title: The Effect of Cimetidine on Serum Concentrations of Piroxicam

The purpose of this 3 week research study is to determine whether cimetidine (Tagamet®), a drug used in the management of peptic ulcer disease, causes an increase in the blood concentration of piroxicam. Piroxicam is a drug used to relieve pain and inflammation associated with such disorders as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, etc.

Prior to beginning the study, you will undergo a medical evaluation to insure that you meet the requirements for this study and are not at unusual risk for serious toxicity if you participate. This evaluation will include a physical examination and medical and medication histories. In addition, approximately 1 tablespoonful of blood will be obtained by venipuncture (inserting a needle into a vein) and a urine sample will be collected in order to perform some laboratory studies. If found eligible to participate in this study, you will be scheduled to come to the hospital one morning to receive 20 milligrams of piroxicam by mouth. Seven milliliters (about 1½ teaspoonful) of blood will be drawn before the piroxicam dose and then at regularly scheduled times over the next 96 hours, (4 days). A total of 18 blood samples will be obtained during this time (approximately 8½ tablespoonfuls of blood). These blood samples will be obtained by either venipuncture (inserting a needle into a vein) or temporarily implanting a heparin lock (a needle which is flushed with an anticoagulant regularly) into a vein from which blood will be drawn. You will also be asked to collect all your urine for 7 days following the piroxicam administration. You will then begin taking cimetidine 300 milligrams four times a day for the next 14 days, to be taken by mouth, with each meal and at bedtime. After taking cimetidine for 7 days you will return to the hospital and once again take 20 mg. of piroxicam. Blood samples and urine will be collected in a manner identical to the procedure described above. During this 3 week study the total amount of blood obtained will be approximately 8 ounces (about 1 cup).

You will be asked not to take any medications, other drugs, or alcohol while you are participating in this study and for 2 weeks before receiving the first dose of the piroxicam. If you use tobacco, are currently taking medications, or are allergic to aspirin, piroxicam, or cimetidine you should not participate in this study.

The two medications used in this study are being used clinically and have been approved by the Food and Drug Administration for use in the United States. The most common side effects or discomforts associated with the use of piroxicam are abdominal pain, heartburn, nausea, vomiting and fluid retention. These are not usually serious and will usually resolve without treatment. Rare but more serious side effects include stomach ulcers, intestinal bleeding and decreased kidney function. These are very unlikely to occur following single doses of piroxicam. Adverse reactions that may occur

during cimetidine therapy include headaches, dizziness, rashes, drowsiness, transient increases in laboratory measures of liver function and kidney function, and reduction in sperm counts. These are usually not serious and resolve following discontinuation of the drug. A potentially serious but rare side effect of cimetidine is development of slow heart rate.

Your participation in this study is completely voluntary. However, because of the pain, discomfort, amount of time involved, and inconveniences that you will endure because of participating in this study, you will be reimbursed up to $75.00 for satisfactorily completing all phases of this study. If, for some reason, you discontinue this study prematurely, you will be reimbursed according to the length of time you participate in this study. You may be withdrawn from the study at any time, either by your decision or your physician's decision without penalty or loss of benefits pertaining to future treatment. In addition, refusal to participate in this study will involve no penalty or loss of benefits. The data obtained from the study will be used for medical and scientific purposes, including publication. During the study, representatives of the Food and Drug Administration may review your medical records. All information will remain strictly confidential.

The laboratory tests are performed during this study as a precaution to decrease the possibility of injury. However, these precautions do not eliminate all possibilities of injury. In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe that you have suffered a physical injury as a result of participation in this research program, please contact the Office of Research Administration, phone number: (801) 581-6903.

Should you have further questions pertaining to the study, your rights as a participant in this study, or experience any problems during the study, please contact Dr. John R. Ward or Dr. Stephen Dahl, phone number: (801) 581-7724.

I _____, agree to participate in this research study which is entitled "The Effect of Cimetidine on Serum Concentrations of Piroxicam". By signing this form, I also acknowledge that I have had the opportunity to ask questions about the procedures, risks, and other items that are involved in this trial.

_____ _____
PATIENT'S SIGNATURE DATE

_____ _____
WITNESS'S SIGNATURE INVESTIGATOR'S SIGNATURE

SCREENING VISIT

THE EFFECT OF CIMETIDINE ON SERUM CONCENTRATIONS OF PIROXICAM

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

AGE: _____

DATE OF EXAM: __/__/__/
M D Y

Vital Signs, Height and Weight:

TEMP: _____°F RR _____/ min PULSE _____/min

B/P: _____/_____mmHg
syst diast

HEIGHT: _____ in (_____cm)

WEIGHT: _____ lb (_____kg)

IBW (calculated): _____kg

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

PHYSICAL EXAMINATION

	Normal 1	Abnormal 2	Describe Abnormality
1. Head, Neck and Thyroid			
2. Ear, Nose and Throat			
3. Eyes			
4. Chest			
5. Lungs			
6. Heart			
7. Lymph Nodes			
8. Abdomen			
9. Anorectal			
10. Genitalia			
11. Skin			
12. Musculoskeletal			
13. Neurological			
14. Other _____			

COMMENTS: _____

Physician's Signature Date

_____ _____

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

MEDICAL HISTORY:

SOCIAL HISTORY:

Smoker: _____Y _____N

Drinker: _____y _____N (if yes describe) _____

MEDICATION HISTORY:

Medication	Dose	Dates Started	Stopped	Reason

ALLERGIES:

APPENDIX 2

ADVERSE REACTIONS:

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

DATE: ___/___/___/
M D Y

*INTENSITY RATING SCALE:
1 = MILD – Awareness of sign or symptom but easily tolerated
2 = MODERATE – Discomfort enough to cause interference with usual activity
3 = SEVERE – Incapacitating with inability to work or do usual activity

NATURE OF ADVERSE REACTION OR INTERCURRENT ILLNESSES	DATE OF ONSET mo/day/yr	DURATION since last visit (# of days)	MAXIMUM INTENSITY	ACTION TAKEN REGARDING TEST DRUG 1 = None 2 = Discontinued 3 = Dosage Reduced 4 = Interrupted	WAS THE ADVERSE REACTION SERIOUS? 1 = No 2 = Yes	DID THE TEST DRUG CAUSE THE ADVERSE REACTION 1 = Definitely Not 2 = Probably Not 3 = Possibly 4 = Probably 5 = Definitely	PATIENT OUTCOME TO DATE 1 = Recovered – No Residual Effects 2 = Adverse Reaction Still Present – No Treatment 3 = Adverse Reaction Still Present – Being Treated 4 = Residual Effects Present – No Treatment 5 = Residual Effects Present – Being Treated 6 = Died (Give details on Death Form)

COMMENTS _____

APPENDIX 3

CIMETIDINE (TAGAMET®) ADMINISTRATION LOG:

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

DATE CIMETIDINE STARTED: _____

LAST DAY OF CIMETIDINE THERAPY: _____

DAY	DATE	TIME CIMETIDINE TAKEN				DOSES MISSED Y/N	S.E. Y/N
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							

PIROXICAM SAMPLE COLLECTION:

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

DATE: ___/___/___/
M D Y

Pre-Cimetidine: _____ Post-Cimetidine: _____

Piroxicam 20 mg taken at: _____ (= TIME 0)

Breakfast taken at: _____

Blood Samples:

Intervals	Date	Scheduled Time	Actual Time	Code
0				
0.5				
1				
1.5				
2				
2.5				
3				
3.5				
4				
6				
9				
12				
24				
36				
48				
60				
72				
96				
168				

SUBJECT INITIALS: __/__/__/ SUBJECT NO: __/__/__/

Urine Samples:

	DATE	URINE VOLUME	COMPL/INCOMPL		CODE
Day 1	_____	_____	_____	_____	_____
Day 2	_____	_____	_____	_____	_____
Day 3	_____	_____	_____	_____	_____
Day 4	_____	_____	_____	_____	_____
Day 5	_____	_____	_____	_____	_____
Day 6	_____	_____	_____	_____	_____
Day 7	_____	_____	_____	_____	_____

APPENDIX 5

APPENDIX 5

1) Ideal Body Weight

$$\text{Ideal Weight (kg)} = 50\text{kg} + 2.3\ \text{kg/inch}\ [\text{Height(inches)} - 60]$$

2) Half-life (t1/2)

$$T1/2 = \frac{0.693}{kel}$$

3) Area under the serum concentration versus time curve (AUC):

a) linear trapezoidal method:

$$AUC_1 = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1})$$

b) logarithmic trapezoidal method:

$$AUC_2 = \frac{(C_{m-1} - C_m)\ (t_m - t_{m-1})}{\ln C_{m-1} - \ln C_m}$$

c) extrapolation:

$$AUC_3 = \frac{Cp_x}{kel}$$

Cp_x = last measurable data point

4) Type II error:

$$Z_\beta = \frac{Z_\alpha - \delta \sqrt{n}}{\sigma}$$

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